REMARKS

I. Status of the Claims

Claims 83-88, 92, 100-103, 106 and 107 are pending in the present application.

II. Miscellaneous

The Examiner indicates (in the August 23, 2001 Office Action, herein "final Office Action") that Applicants have not complied with the request for copies and/or English language translations of references AC2, AN2 and AO2. Applicants submitted copies of these documents, including an English abstract for AO2 (i.e., AT24). These papers appear to have been separated from the file. Applicants again provide documents AC2, AN2 and AO2. Applicants also provide a copy of the postcards stamped by the PTO indicating that these documents have been filed twice (date-stamped June 14, 2001 and September 19, 2001).

III. Rejections

A. Rejection Under 35 U.S.C. § 112, Second Paragraph

On page 3 of the final Office Action, claims 83-88, 92, 100-103, 106 and 107 are rejected as indefinite. Applicants traverse the rejection.

Claims 106 and 107 are rejected as being indefinite for reciting "portion thereof" on the grounds that the phrase is unclear. Applicants point out that claim 106 is based on canceled claim 81. Claim 81, step (c), recited "over-expressing an endogenous gene or a portion thereof." Applicants believe that it would have been clear that over-expression of a "portion" referred to over-expression of a portion of the gene.

The Examiner must have previously considered step (c) to be definite since claim 81 was not rejected in the non-final Office Action mailed February 14, 2001, for reciting "portion thereof." Step (c) in claim 106 similarly recites "over-expression of said protein encoded by said endogenous cellular gene or portion thereof." The phrase "portion thereof" is also found in the preamble of claim 106 to be consistent with step (c). Applicants believe that in view of step (c), the phrase in the preamble is clear.

Part of the Examiner's argument is that portions do not ordinarily encode proteins. *See* page 3 of the final Office Action. Applicants point out, however, that portions of genes do encode proteins. For example, exon I often does not contain any coding sequences. The vector can integrate downstream of exon I. In this case, the primary transcript produced by transcription from Applicants' vector does not contain the entire RNA sequence found in the naturally-occurring primary transcript. However, a shortened primary transcript will not affect the translation product because no coding sequence is lost from this transcript. Accordingly, "portions" of genes do ordinarily encode proteins and the Examiner's assertion is unfounded. To the extent that the rejection is based on the erroneous assumption, the rejection is improper and should be withdrawn.

On page 3 of the final Office Action, claim 107 is rejected as being indefinite in the recitation of the term "detecting." The Examiner takes the position that the claim must recite *how* detection is done to be definite. Applicants disagree. This term has a plain dictionary meaning. Thus, Applicants question why the Examiner believes that a person of ordinary skill in

the art, having access to an English dictionary, would not understand what the term means. Since the meaning is clear, Applicants submit that if a person of ordinary skill in the art practiced steps (a), (b) and (c) and then detected over-expression of the gene by ANY means, they would know that they had infringed the claims even though no specific method of detection is recited.

In view of the above discussion, Applicants submit that the grounds of rejection have been addressed and the rejection overcome. Reconsideration and withdrawal of the rejection is respectfully requested.

B. Rejection Under 35 U.S.C. § 112, First Paragraph: Written Description

On page 4 of the final Office Action, claim 107 is rejected on the grounds that the method of "detecting over-expression of an endogenous cellular gene in a cell introduced in an animal" is unsupported (final Office Action, page 4). Applicants traverse the rejection.

The Examiner requests that Applicants point out support for the claimed method. First, Applicants point out that claim 107 is based on canceled claim 82. Step (d) in claim 82 was directed to "*screening* said cell for over-expression of said endogenous gene" (emphasis added). The Examiner did not consider "screening" to be new matter. "Screening" for a gene inherently discloses "detecting." Accordingly, "detecting" should not constitute new matter.

Applicants also submit that support for the method of "detecting" is inherent where Applicants disclose screening for expression of a gene product in an animal. *See, e.g.,* specification, page 7, lines 24-30, through page 8, lines 1-8; page 8, lines 15-23; page 9, lines 7-

13; page 10, lines 22-30; page 11, lines 20-25; page 32, lines 1-8; page 35, lines 23-30, through lines 1-2 on page 36; page 36, lines 12-19; page 36, lines 28-30, through page 37, lines 1-4; and page 35, lines 21-26.

Accordingly, Applicants submit that the method for "detection" finds adequate support in the specification. Reconsideration and withdrawal of the rejection is respectfully requested.

C. Rejection Under 35 U.S.C. § 112, First Paragraph: Enablement

On page 5 of the final Office Action, claims 83-88, 92 and 100-103 remain rejected and claims 106 and 107 are rejected under 35 U.S.C. § 112, first paragraph, "for the reasons of record." Applicants respectfully traverse the rejection.

The Examiner's position is that Applicants disclose protein production in a cell introduced into an animal, but only for cell therapy, and that there is no other well-established utility. The Applicants' position is that Applicants disclose cell therapy only as an example (*see* Exhibit A) and that the non-therapeutic utility of protein production from a cell introduced into an animal is well-established (readily apparent). Applicants also point out that isolation of proteins from such cells is disclosed and that the utility of such isolation is well-established.

To support their position, Applicants previously provided an expert's opinion in the form of a Declaration filed June 14, 2001. The Declarant cited numerous references supporting his conclusions. The Examiner, however, asserted that claim 106 is the same scope as previously examined claim 81 and rejected the claim for the reasons of record (final Office Action, page 5).

The Examiner indicated that Applicants' arguments and Declaration "*have been fully considered*" (emphasis added) but are not persuasive (final Office Action, page 6). Applicants do not agree.

The Examiner has not fully considered the declaratory evidence. The Examiner considered only Applicants' Declaration and failed to consider the supporting references in full. Based on the Declaration, *not supporting evidence*, the Examiner dismissed the Declaration as unpersuasive. Thus, the Declaration was not fully considered and was improperly dismissed as unpersuasive.

The Examiner states that the references supporting the Declaration were neither supplied nor listed in a PTO Form 1449. The references were, in fact, supplied. Applicants herewith provide a copy of Applicants' postcard which was stamped by the PTO on June 14, 2001, showing that the references were received by the PTO.

The Examiner improperly rejected the Declaration for another reason. The Examiner rejected the expert Declarant's conclusions without showing deficiency in the Declarant's expertise, sufficiency of the Examiner's own expertise, or incorrect scientific facts. It is improper for the Examiner to substitute his opinion for that of the expert Declarant without such evidence.

As "evidence" for the "deficiency" of the declaratory evidence, the Examiner stated that Point 8 (that relates to introducing hybridomas into an animal to produce antibodies) "does not

appear to be germane" (final Office Action, page 7). His reason is that Applicants' specification "does not disclose or provide any nexus for *in vivo* introduction of hybridomas" (final Office Action, page 7). He concludes that, "[a]bsent evidence to the contrary, there is no evidence to suggest that one skilled in the art would have had any reason to construe the claimed disclosure as embracing methods for producing antibodies from hybridomas introduced into animals" (final Office Action, pages 7-8). Applicants respectfully disagree because they provided evidence to the contrary which the Examiner failed to address.

First, the specification discloses production of a desired protein in an animal *in vivo*. *See* the text in Exhibits A and B. Next, the specification discloses hybridomas as a desired host cell for expressing an endogenous gene. *See* Exhibit C. Next, the specification discloses expressing antibodies from Applicants' cells as a desired protein. *See* Exhibit D and Point 8 in the Declaration. The Declarant cited the Applicants' *earliest effective priority* document. The supporting reference for Point 8 disclosed producing antibodies in an animal using cells that were genetically-engineered. Applicants submit that based on Applicants' disclosure cited above and in view of the cited art, it would have been readily apparent that Applicants' cells could also be useful for producing antibodies in an animal.

As further "evidence" for the "deficiency" of the declaratory evidence, the Examiner argues that the disclosures of U.S. Patent No. 5,641,670 and U.S. Patent No. 5,733,761 (Declaration, pages 5-7, Point 9) "fail to establish a nexus between the claimed methods of the instant invention and the *claims* deemed to be enabled by the issued patent" (emphasis in original) (final Office Action, page 8). Applicants submit that the *claims* in these patents are

irrelevant. The *disclosures* were presented as evidence of well-established utility of non-therapeutic protein production from cells introduced into an animal. These patent specifications show how recombinant cells can be used in the real world. They state that such cells can be used to immunize animals to produce antibodies, to produce hormones for dairy production, and to produce antibodies that can be further used for diagnostic and therapeutic purposes. Applicants submit that the disclosures are evidence for the utility of such protein production. Applicants also submit that whether expression is achieved by an exogenous coding sequence, homologous recombination or non-homologous recombination, the usefulness would have been readily apparent.

The Examiner finally argues (page 8 of the final Office Action) that "it is generally noted for the record, that the alleged disclosures described by co-inventor Harrington appear to be directed to methods with different and distinct purposes, relying on specific products, lacking any clear nexus to the instant application, particularly since none of the products or methodologies disclosed therein appear to be described in the instant application." Applicants disagree. The Examiner appears to have lost sight of how the references are to be properly applied. They should be applied as evidence to address the Examiner's position that there is no well-established, non-therapeutic utility for producing protein from cells introduced into an animal. The references do disclose methods with "different and distinct purposes" that produce "specific products," but they <u>all</u> provide evidence of non-therapeutic protein production from cells introduced into an animal. The proteins that are produced vary from reference to reference and the ultimate purpose of expression varies from reference to reference, but such variance does not defeat the reason that the references were offered in the first place: to show that the art

practiced non-therapeutic protein production from cells introduced into an animal. The "nexus" is that Applicants disclose protein production from a cell introduced into an animal and the references show that there is a well-established utility for non-therapeutic protein production in an animal. Since a person of ordinary skill in the art is presumed to have knowledge of the literature, the uses would have been readily apparent to a person of ordinary skill in the art reading Applicants' disclosure of using Applicants' non-homologously recombinant cells to express protein in an animal.

Accordingly, the Examiner's rejection is improper because (1) he failed to consider the references, (2) he failed to correctly apply the information in the references that he attempted to consider and (3) he substituted his opinion for that of an expert declarant without sufficient scientific or legal reason.

Applicants respectfully submit that Applicants' Declaration and evidence should have overcome the Examiner's rejection in the non-final Office Action. The Examiner has not presented evidence to rebut the Declarant's opinion based on the supporting references that a person of ordinary skill in the art would have readily recognized the utility of Applicants' claimed methods. Reconsideration and withdrawal of the rejection is, therefore, respectfully requested.

The Examiner also asserts that Applicants' arguments regarding utility are not germane because no utility rejection was made. Applicants point out, however, that the basis for the Examiner's rejection was lack of utility. The Examiner's rationale for rejecting the claims was

that the only disclosed utility in Applicants' specification is cell therapy and cell therapy is not enabled. Accordingly, the rejection was based on the assumption that the specification lacks any other disclosed utility. Applicants include, as Exhibit F, the Examiner's discussion from the non-final Office Action with highlighted sections showing the Examiner's rationale as lack of utility. Since the Examiner based the rejection on a lack of utility, Applicants submit that their arguments and Declaration are germane.

The Examiner continues to base the rejection on a lack of disclosed utility by applying the test for well-established utility and asserting that the claims fail the test. On page 6 of the final Office Action, the Examiner argues as follows:

> The claims are considered in light of the specification, wherein the *only readily apparent use* disclosed is for cell therapy which is not enabled for the reasons of record, the grounds of which have not been disputed by Applicants. There is no other specifically disclosed use for the methods. In as much as the claimed methods read on cell therapy, which has a well-established utility, no utility rejection was made.

(Emphasis added). By arguing that the only "readily apparent" use disclosed is cell therapy, the Examiner applies the test for a well-established utility and concludes that the disclosed use (i.e. protein production in an animal) fails the test.

Since the rejection in the non-final Office Action was based on the position that the only disclosed utility was cell therapy, Applicants disputed this assertion in their June 14, 2001, response. Applicants argued that the specification discloses protein production in cells

introduced into an animal and that this has a well-established utility. Applicants submitted a Declaration and supporting references as evidence to support the Declarant's conclusion.

The Examiner also asserts that the claims are not limited to non-therapeutic protein expression. Applicants point out that this argument is not relevant. The Examiner bases the rejection on the assumption that non-therapeutic protein expression from cells introduced into an animal does not have a well-established utility. Therefore, even if the claims contained this feature, the Examiner's rationale would still apply. The issue still would be whether there is a well-established utility for non-therapeutic protein expression.

The Examiner also asserts that "despite reference to cell-based protein production, isolation and purification, no such steps are recited in the claimed methods" (final Office Action, page 7). This argument is also not on point for the reason discussed directly above. Moreover, the claims do, in fact, recite cell-based protein production. The claims recite explicitly that the non-homologously recombinant cell is maintained in the animal under conditions appropriate for over-expression of the protein and that the protein is produced in the animal. *See* claims 106 and 107, step (c), last 3 lines.

The Examiner also argues that isolation and purification steps should be recited in the claims to overcome the rejection. Applicants disagree. The Examiner recognizes the utility of isolating and purifying protein using Applicants' claimed methods. This isolating and purifying of protein is disclosed in Applicants' specification *and* is a well-established utility (as evidenced by the references that support the Declaration). Because the claimed methods are disclosed as

being useful for isolating and purifying protein and because isolating and purifying protein from cells introduced into an animal is well-known in the art, Applicants' method *as claimed* has utility.

The Examiner also argues that there is no evidence of record to support Applicants' assertion that the specification also discloses the isolation and purification of protein produced in an animal by the cells of the invention. The Examiner does not, however, explain this statement. In Applicants' response filed June 14, 2001, Applicants cited in detail the assertions of utility in Appl. No. 08/941,223, the *earliest effective priority* application. Accordingly, it is unclear why the Examiner has indicated that there is no evidence of record to support the assertion. (In an interview with Examiner Shukla (who has taken this case over from the previous Examiner), Examiner Shukla requested that Applicants cite the specification of Appl. No. 09/513,997. The Examiner is, therefore, directed to Exhibit B.)

The Examiner also bases the dismissal of Applicants' arguments and declaratory evidence on the position that there is no evidence of record that the process for producing proteins in an animal is *routinely performed* in the art. This is not the test, however. The test is whether the utility would have been "readily apparent." Dr. Harrington concluded that it would have been.

In view of the above discussion, Applicants submit that the Examiner's rationale for the rejection is in error. Reconsideration and withdrawal of the rejection is respectfully requested.

D. Rejection Under 35 U.S.C § 102(e)

On page 9 of the final Office Action, claims 83, 86, 87, 92, 101 and 102 remain rejected and claim 106 is rejected under 35 U.S.C. § 102(e) as being anticipated by Sands *et al.* (U.S. Patent No. 6,136,566, herein "Sands") and Vasallo *et al.* (*Bioch. Biophys. Res. Commun. 270(3):* 1036-1040 (April 2000), herein "Vasallo"). Applicants respectfully traverse the rejection.

(1) Vasallo cannot be used as art. Vasallo, according to the Examiner, published April 2000. Applicants' latest priority application was filed as a divisional application on February 25, 2000. Moreover, the parent application on which the divisional application is based was filed March 26, 1999. Accordingly, Vasallo cannot be used as art.

(2) The Examiner rejects the claims based on an additional argument that would have applied to the previously-submitted claims. Therefore, the argument should have been presented earlier. A final rejection was improper. The new point of argument is that the phrase "or portion thereof" is the reason that the claims are (allegedly) anticipated by Sands.

The Examiner's argument is as follows: "[t]o the extent that the claims read on 'portion thereof,' the vectors of Sands designed to over-express marker proteins, anticipate the subject matter as claimed" (final Office Action, page 10). This phrase was, however, in claim 81. *See* step (c) in canceled claim 81. Accordingly, based on the Examiner's reasoning, this argument could have been submitted earlier and final rejection was improper.

(3) Even if Vasallo had an effective date, the rejection should not be sustained. The Examiner's reliance on the phrase "or portion thereof" to reject the claims as anticipated is in error. The Examiner asserts that Sands teaches a method for introducing a non-homologously recombinant cell (for example, an embryonic stem cell) into an animal. He then asserts that Sands uses a vector that over-expresses a marker protein. He reasons that the marker protein is a "portion" of an endogenous cellular gene because "it contains the same amino acids (i.e. portions) that are present in any endogenous cellular protein" (final Office Action, page 10). He then concludes that this disclosure anticipates the claims. Applicants respectfully disagree.

First, the Examiner has not presented any evidence that the Sands marker contains amino acid sequences that are homologous to an endogenous gene. For this reason alone, the reference fails.

But even if the marker had homology to an endogenous gene, the claims contain features that distinguish the invention from Sands. Sands fails to disclose that the transcriptional regulatory sequence becomes operably-linked to an endogenous gene and, as a result of the linkage, causes over-expression of protein from that endogenous gene. Applicants' claim 106, however, recites this feature. Claim 106 recites that the transcriptional regulatory sequence becomes operably-linked to the endogenous gene when the vector integrates and that this endogenous gene is thereby over-expressed. Accordingly, even if the marker on the Sands vectors had homology to an endogenous gene, expression of the marker does not meet the claimed features because expression of the marker is not the result of operable linkage with the

transcriptional regulatory sequence that occurs upon vector integration. It is already operably linked.

Further, Sands does not teach or suggest the production of *protein* from the endogenous cellular gene that becomes operably linked to the transcriptional regulatory sequence following integration. In fact, the Sands vectors are specifically designed to prevent such protein expression. *See* Applicants' June 14, 2001, response, page 24 (Exhibit E). For this reason alone, Applicants submit that reliance on Sands is erroneous. Reconsideration and withdrawal of the rejection is respectfully requested.

E. Rejections Under 35 U.S.C. § 103

1. On page 11 of the final Office Action, claim 107 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Sands for the reasons applied to claims 83, 86, 87, 92, 100-102 and 106 as above and for the reasons set forth in the final Office Action on page 11. Applicants respectfully traverse the rejection.

Sands fails as a primary reference since it is improperly relied upon per the reasons discussed above. Furthermore, as Applicants discussed in their June 14, 2001, response, it would not have been obvious to modify the Sands vectors to produce protein since Sands explicitly designed the vectors so that they could not produce protein from the endogenous cellular gene that is transcribed. *See* Applicants' June 14, 2001, response, pages 22-24, particularly page 24 (Exhibit E). Reconsideration and withdrawal of the rejection is respectfully requested.

2. On page 11 of the final Office Action, claims 83-85 remain rejected and claim 106 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Sands in view of Schmidt *et al.* (*Mol. Cell. Biol. 10(8):* 4406-4411 (August 1990), herein "Schmidt"). Applicants traverse the rejection.

The Examiner asserts that Sands is relied upon as above. Since this reference fails as a primary reference, the rejection cannot stand unless the deficiency is met by the secondary reference. However, Schmidt is relied upon to teach the CMV enhancer/promoter. Since Schmidt does not compensate for the deficiencies of Sands, Applicants submit that the rejection is improper and should be withdrawn. Reconsideration and withdrawal of the rejection is respectfully requested.

3. On page 12 of the final Office Action, claims 83 and 87 remain rejected and claim 106 is rejected under 35 U.S.C. § 103(a) and being unpatentable over Sands in view of Bujard *et al.* (U.S. Patent No. 5,912,411, herein "Bujard"). The Examiner states that the claims are rejected for the reasons set forth in the non-final Office Action and further set forth in the final Office Action. Applicants respectfully traverse the rejection.

Sands is relied upon as above and, therefore, fails as a primary reference. Bujard is relied upon only for teaching transgenic mice with a tetracycline-inducible promoter. Since Bujard does not compensate for the deficiencies of Sands, Applicants submit that the rejection is improper and should be withdrawn. Reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

It is believed that a full and complete response has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

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Date: April 16, 2002

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